and weak affinity for wild-type MarA. Early results suggest that even minimal reorganization in the core can generate novel protein binding specificity.

136-Pos

Global Conformational Change Induced By Single Amino Acid Residue of Photoactive Yellow Protein in Time Domain

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We studied the conformational changes of protein from view point of the diffusion coefficient change. We successfully monitored that the photocycle kinetics of site directed mutants and compared the results with wild-type PYP. The role of isomerization and effect of surrounding amino acid residues during photocyle were investigated. The replacement of Lys by a small Ala residue remarkably altered the conformation of protein. The details of the experiments will be discussed later.

137-Pos

Exploration of Free-Energy Profiles With Conformational Changes of Proteins

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Under physiological conditions, proteins fluctuate around their native state and often undergo conformational changes on interacting with ligands. Thermal fluctuations are critical to the dynamics of nanoscale structures like proteins, and conformational changes can stabilize the binding energy of these molecules; therefore, both these factors are crucial for the retention of protein function. Recently, X-ray crystallographic studies have revealed conformational differences between the liganded and unliganded states of proteins. The conformational transition induced in proteins upon ligand binding can be explained by 2 representative models, the induced-fit model and the preexisting equilibrium dynamics. However, it remains unclear as to whether these models appropriately describe the actual dynamics of proteins.

Here, we performed molecular dynamics (MD) simulations for the lysine/arginine/ornithine (LAO)-binding protein and the maltose-binding protein (MBP). We used the umbrella sampling approach to examine the free-energy profiles governing the conformational changes induced in these proteins upon ligand binding. The conformational transition mechanisms of LAO-binding protein and MBP are believed to differ, being characterized by the preexisting equilibrium dynamics and the induced-fit model, respectively. However, our results revealed that the conformational transition mechanism of LAO-binding protein is based on a combination of the preexisting equilibrium dynamics and the induced-fit model, rather than solely on the former, while the mechanism of MBP is based mainly on the induced-fit model. And it was also suggested that the fluctuations in the apo state are important for the conformational changes and the protein function in both of these proteins.

138-Pos

Large-Scale Conformational Sampling of Proteins Using Temperature-Accelerated Molecular Dynamics

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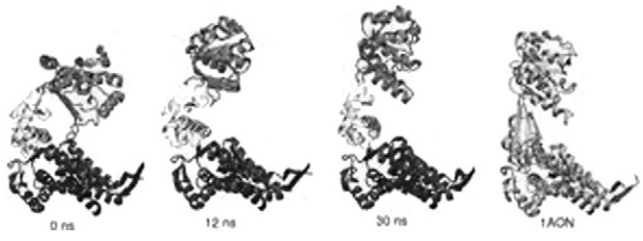
An adaptation of temperature-accelerated molecular dynamics (TAMD) is presented which permits conformational sampling of multidomain proteins in all-atom, explicitly-solvent molecular dynamics simulations. The method is simple to implement, requires no target bias, and is designed to allow the system to hyperthermally explore the free-energy surface in a given set of collective variables computed at the physical temperature. Our collective variables are Cartesian coordinates of centers of subdomains identified using a structure-based clustering algorithm. The method is applied to the GroEL subunit in its t-state, and the HIV-1 envelope gp120 in its sCD4/17b-bound state. For GroEL, the method induces in about 40 ns conformational changes that substantially recapitulate the t-to-r″ transition: the apical domain is displaced by more than 30 Angstroms, with a twist of almost 90 degrees, and RMSD relative to the r″ conformer is reduced from 13 to below 5 Angstroms, representing a fairly high degree of predictive capability. For gp120, the method predicts a conformational transition involving realignment of inner and outer domains to expose residues distal to the bridging sheet. The method gives an estimate of 10 kcal/mol for the free energy barrier between conformers in both cases.



139-Pos

Molecular Dynamics Simulation Study of Isolated Hamp Domain

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The HAMP domain is a linker region in prokaryotic sensor proteins which functions in two-component signal transduction pathways. HAMP exhibits a parallel coiled coil motif comprising four helices and transfers the signal from the sensor domain to the transmitter domain, usually a kinase. We present MD simulations of isolated HAMP (from A. fulgidus) in both the activated state and the inactive state, using structural data from wild type and mutant HAMP domains. Our simulations show that subtle changes in the hydrophobic core of HAMP lead to larger rearrangements in the coiled coil complex. The implications of these results for other signal transduction proteins containing HAMP are discussed.

140-Pos

Application of Linear Response Theory on Protein Networks For Identifying Allosteric Transitions

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We developed a fast and accurate method to predict residues that play an important role in allosteric transitions of single protein domains called perturbation response scanning (PRS). This method treats the protein as an elastic network and uses linear response theory (LRT) to obtain the residue fluctuations upon external perturbation. By sequentially exerting directed random forces on single-residues along the chain of the unbound form (i.e. by perturbing each residue one by one along the chain) and recording the resulting relative changes in the residue coordinates using LRT, we can successfully reproduce the residue displacements from the experimental structures of bound and unbound forms. Rigorous analysis of the response fluctuation profiles upon random perturbation of each residue, we identify the highest response residues that mediate long-range communication in proteins. Based on a structural network without reference to the dynamics of the bound forms, a dominant intermolecular signaling pathway of PDZ domain proteins (PSD-95 and hPTP1E) and cAMP-dependent protein kinase (PKA) can be identified.

This method can determine not only residues that play an important role in allostery but can be utilized to determine multiple receptor conformation for flexible docking scheme.

141-Pos

Orientation Dependent Residue Energies For Proteins Coarse-Grained From Atomic Force Fields

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Coarse-grained models for protein simulations can potentially access longer time-scales in larger protein systems than atomic level models. Here, a coarse-grained residue-pair potential, with distance and orientation dependency, is derived from equilibrium ensembles of residue pairs generated by molecular dynamics (MD). In particular, the Boltzmann inversion method is used to determine the energies. The residue-pair potential is used in the folding simulations of six small proteins, (28-67 residues) containing a variety of secondary structures. For the proteins tested, folding simulations by Monte Carlo methods generates structures similar to the native ones. However, these native like structures were among the lowest in energy for alpha helical proteins but not for proteins containing extended beta structures. It is also found that a careful balance between local and non-local interactions is essential.

142-Pos

Conformational Control of Ubiquitination in the Cullin-Ring E3 Ligase Machinery

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Tagging proteins by polyubiquitin is a key step in protein degradation. Cullin-RING E3 ubiquitin ligases (CRLs) facilitate ubiquitination by transfer ubiquitin from ubiquitin-conjugating enzyme E2 to the target protein. Neddylation by conjugation of ubiquitin-like protein NEDD8 to cullin can stimulate ubiquitination process. However, crystallography indicates a 25-35 Å distance between neddylation activate sites and a 50-60 Å distance between